Intramolecular Cobalt-Catalyzed [2+2+2] Cycloaddition of O-Protected Diyne-Cyanohydrins

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Abstract: O-Protected cyanohydrins were found to serve as a source of the nitrile within the intramolecular cobalt-mediated [2+2+2] cycloaddition to pyridines. Several 6-substituted 1,2,3,4,7,8,9,10-octahydrophenanthridines were synthesized using this cycloaddition of diyne-cyanohydrins. By introduction a TMS group a divergent way to such phenanthridine derivatives was elaborated.

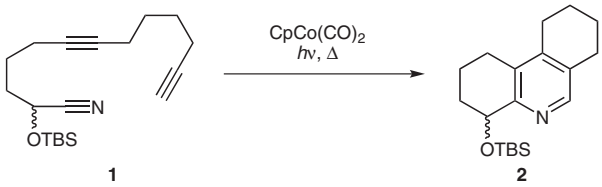
Key words: cyanohydrin, cycloaddition, pyridines, alkynes, heterocycles

The cobalt-mediated [2+2+2] cycloaddition has already been proven to be a powerful tool in organic synthesis.[1] Especially intermolecular cycloadditions to polycyclic benzene derivatives as well as to pyridines have widely been explored.[1,2] Nevertheless, the regioselectivity of this intermolecular approach has always been problematic, although several electronic and steric effects take certain influence on this issue.[1f,p] To solve this problem, several intramolecular alternatives have been developed.[1i,l,3] However, to build up pyridine rings intramolecularly, a nitrile group has to be introduced into a diyne, which often causes problems.

To facilitate this challenge, based on previous work of Chelucci and co-workers,[4] Heller et al.,[5] and the Kotora group,[6] we tried to introduce the nitrile group via an O-protected cyanohydrin, which is usually built up much more easily.

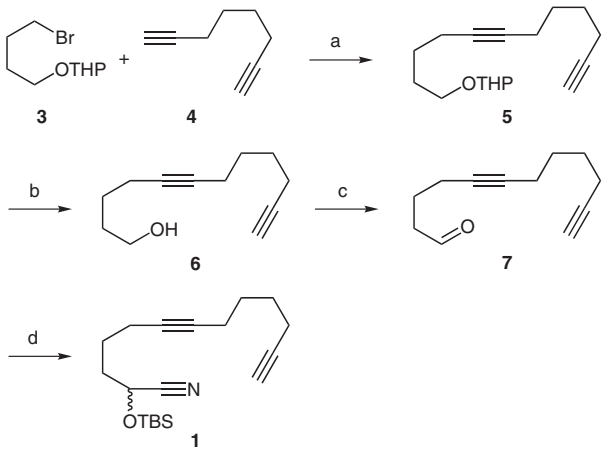
Herein we wish to present the [2+2+2] cycloaddition of O-protected diyne-cyanohydrins to diverse substituted octahydrophenanthridines catalyzed by a cobalt catalyst.

A nitrile group embedded in a cyanohydrin has an electronical environment which is quite different from that of an alkyl nitrile group. Hence, we wondered if a cyanohydrin would be able to provide the nitrile group for the cycloaddition. Therefore, we designed a model system containing no other functional groups than two triple bonds and the cyanohydrin connected by alkyl bridges (Scheme 1). In order to avoid problems caused by an unprotected alcohol group of the cyanohydrin, which could coordinate to the metal of the catalyst, we decided to work with an O-protected cyanohydrin taking the risk of sterical hindrance disturbing the cycloaddition in account.



Scheme 1 Model system for the cycloaddition of diyne-cyanohydrins

The synthesis of compound **1** could be started in analogy to a sequence elaborated by Slowinski et al.[7] Hence, we started from 1,7-octadiyne **4** which was coupled with 4-bromobutanol protected as a THP ether (compound **3**).[8] Within this coupling HMPA could successfully be substituted by 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU).[9] Further deprotection of the alcohol group with *p*-toluene sulfonic acid monohydrate and oxidation to the according aldehyde **7** under Swern conditions proceeded smoothly as described by Slowinski. The following transformation of the aldehyde to a cyanohydrin could be done in analogy to a procedure of Rawal and coworkers[10] by in situ generation of TBSCN from TBSCl and KCN using a one-pot procedure. This reaction already resulted in compound **1**, the desired cyclization precursor (Scheme 2).



Scheme 2 Model system for the cycloaddition of diyne-cyanohydrins. *Reagents and conditions*: (a) *n*-BuLi, DMPU, THF, –78 °C to r.t. (66%); (b) PTSA, acetone–H_2O (100:1), reflux; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C to r.t.; (d) KCN, TBSCl, $ZnBr_2$, MeCN (24% over 3 steps).

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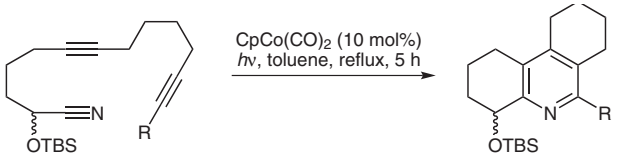
As we did not carry out this synthesis stereoselectively, we got a racemic mixture of compound **1**, which was also used within the cyclization experiments. Since we were interested in the synthesis of aza-naphthochinones starting from **2**, the use of a racemate is unimportant.

Because of its convenient handling $CpCo(CO)_2$ was used as catalyst (10 mol%) for the intramolecular [2+2+2] cycloaddition of the diyne-cyanohydrin **1**. Heating to reflux in degassed toluene under irradiation of a 250 W tungsten lamp yielded the desired product **2** in 40% yield.[11] The successful cycloaddition could easily be confirmed in a recorded ^1H NMR spectrum showing the only pyridine proton at $\delta = 8.15$ ppm.[12] It is important to note, that no elimination of the α-hydroxy group could be observed under these harsh reaction conditions.

Having this first octahydrophenanthridine **2** in hand, we tried to explore the influence of further sterical hindrance within the cycloaddition by the construction of 6-substituted octahydrophenanthridines. Therefore, different groups were introduced at the terminal acetylene of the cyclization precursors (Scheme 3).

To synthesize the precursors for the cycloaddition, a similar route to the one shown in Scheme 2 could be used. The substituents were introduced by alkylation of the bromide with an already substituted diyne. The rest of the synthesis could be done in analogy to the first route described above.

The cyclization of the substituted diyne-cyanohydrins **8** proceeded in good yields up to 78% (Scheme 3). This means, even further sterical bulkyness did not disturb the cycloaddition.



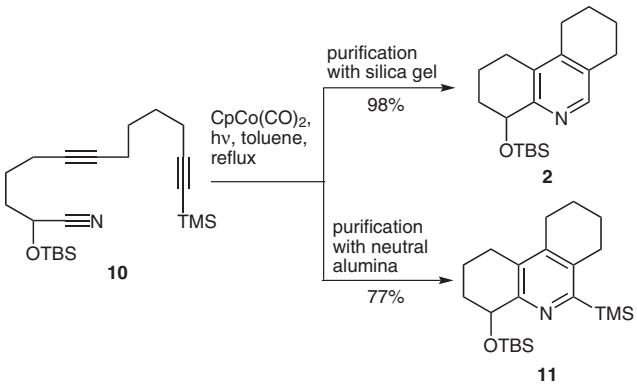
1 R = H
8a R = Me
8b R = Ph

2 R = H 40%
9a R = Me 70%
9b R = Ph 78%

Scheme 3 Cycloaddition of diyne-cyanohydrins to 6-substituted octahydrophenanthridines

As in these cases of 6-substituted octahydrophenanthridines there was no proton at the pyridine ring. Thus, the identification was not as easy as before. 2D NMR spectra and IR spectra, showing no acetylene or nitrile any more, had to be recorded to identify the structures unambiguously. In addition, correct mass spectra and CHN analyses were obtained for this compound as well as for all other ones.[13]

In order to avoid the necessity of a very early introduction of the substituents, we tried to introduce a functionality that could be further derivatized after the cycloaddition. Using 1-TMS-octa-1,7-diyne instead of unprotected octa-1,7-diyne in the synthesis shown in Scheme 1 we could successfully build up a TMS-containing precursor **10** for the cycloaddition. The cycloaddition was carried out as described before in refluxing degassed toluene using 10 mol% $CpCo(CO)_2$ as catalyst under irradiation with a tungsten lamp. When no starting material could be detected by TLC the product was chromatographically purified over silica gel resulting 98% of the unsubstituted cyclization product **2**. Obviously, the desired product was protodesilylated because of the acidic silica gel.[14] The yield of **2** could be improved from 40% up to 98% using the TMS-diyne derivative. The use of neutral aluminium oxide for purification instead of silica gel yielded the desired TMS-substituted octahydrophenanthridine **11** in a 77% yield and only little amounts of the protodesilylated side product (Scheme 4).



Scheme 4 Cycloaddition of the TMS-substituted diyne-cyanohydrin and purification of the cyclization product

This TMS group could now further be substituted or functionalized using various methods, for example, oxidation according to Tamao[15] or Hiyama[16] coupling reaction, which is under current investigation. Thus, a divergent way to 6-substituted octahydrophenanthridines was opened.

In summary, we could demonstrate O-protected cyanohydrins to provide their nitrile group for an intramolecular cobalt catalyzed [2+2+2] cycloaddition. By application of this method several differently 6-substituted octahydrophenanthridines could be built up. The introduction of a TMS group in position 6 of the cyclization product offers the access to a divergent synthetic strategy for the preparation of further 6-substituted octahydrophenanthridines.

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(11) **A Typical Procedure for the Cycloaddition Reaction**
To the diyne-cyanohydrin (0.5 mmol) a solution of $CpCo(CO)_2$ (0.05 mmol) in toluene (15 mL) was added. The reaction mixture was refluxed with contemporaneous irradiation by a 250 W tungsten lamp until no starting material could be detected by TLC. After addition of silica gel and evaporation of the solvent the product was subjected to column chromatography yielding the desired product.

(12) **4-(*tert*-Butyldimethylsilyloxy)-1,2,3,4,7,8,9,10-octahydrophenanthridine (2)**
Yellowish solid; mp 60–62 °C. R_f = 0.43 (petroleum benzene–EtOAc = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.06 [s, 3 H, $Si(CH_3)_2t$-Bu], 0.21 [s, 3 H, $Si(CH_3)_2t$-Bu], 0.89 [s, 9 H, $SiMe_2C(CH_3)_3$], 1.76 (m, 6 H, 3 × CH_2), 1.94–2.13 (m, 2 H, CH_2), 2.37–2.64 (m, 4 H, 2 × CH_2), 2.71 (m, 2 H, CH_2), 4.78 (m, 1 H, H4), 8.15 (s, 1 H, H6) ppm. ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = –4.9, –4.0 [$Si(CH_3)_2t$-Bu], 16.9 (C2), 18.3, 22.2, 22.7, 25.0, 25.5 (C7, C8, C9, C10, and $SiMe_2CMe_3$), 25.9 [$SiMe_2C(C)H_3)_3$], 26.8 (C1), 31.9 (C3), 70.2 (C4), 130.0, 131.3 (C6a and C10a), 144.2 (C10b), 147.4 (C5), 153.8 (C4a) ppm. GC-MS: *m/z* (%) = 317 (1) $[M]^+$, 260 (100) [M – *t*-Bu]$^+$, 186 (16) [M – OTBS]$^+$, 75 (10). IR (neat): 2927.1 (m), 2854.4 (m), 1580.7 (w), 1567.2 (w), 1461.9 (w), 1243.0 (m), 1077.7 (s), 1030.5 (s), 831.2 (s), 777.1 (s) cm^{-1}. Anal. Calcd for $C_{19}H_{31}NOSi$: C, 71.87; H, 9.84; N, 4.41. Found: C, 71.89; H, 9.79; N, 3.50.

(13) **4-(*tert*-Butyldimethylsilyloxy)-6-methyl-1,2,3,4,7,8,9,10-octahydrophenanthridine (9a)**
Yellow wax; R_f = 0.67 (petroleum benzene–EtOAc = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.06 [s, 3H, $Si(CH_3)_2t$-Bu], 0.23 [s, 3 H, $Si(CH_3)_2t$-Bu], 0.90 [s, 9 H, $SiMe_2C(CH_3)_3$], 1.77 (m, 6 H, 3 × CH_2), 1.95, 2.06 (2 × m, 2 × 1 H, CH_2), 2.34 (s, 3 H, CH_3), 2.40, 2.52 (2 × m, 2 × 1 H, CH_2), 2.59 (m, 6 H, 3 × CH_2), 4.75 (t, 1 H, ^3J = 3.6 Hz, H4) ppm. ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = –4.8, –4.0 [$Si(CH_3)_2t$-Bu], 17.5, 18.4 (2 × CH_2), 22.0 (CH_3), 22.3 (CH_2), 22.4 ($SiCMe_3$), 25.0 (CH_2), 26.0 [$SiC(CH_3)_3$], 26.1, 26.4 (2 × CH_2), 32.1 (C3), 70.3 (C4), 127.6, 129.1 (C6a and 10b), 143.9 (C10b), 152.5, 153.5 (C4a and C6) ppm. GC-MS: *m/z* (%) = 331 (1) $[M]^+$, 274 (100), 200(14), 75 (12). IR (neat): 2928.6 (m), 2854.4 (m), 1575.9 (w), 1427.0 (m), 1247.3 (m), 1080.9 (s), 1028.8 (s), 1003.8 (m), 956.8 (m), 877.0 (m), 832.1 (s), 774.2 (s) cm^{-1}. Anal. Calcd for $C_{20}H_{33}NOSi$: C, 72.45; H, 10.03; N, 4.22. Found: C, 71.12; H, 9.76; N, 4.21.

4-(*tert*-Butyldimethylsilyloxy)-6-phenyl-1,2,3,4,7,8,9,10-octahydrophenanthridine (9b)
Colorless solid; mp 116 °C. R_f = 0.70 (petroleum benzene–EtOAc = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05 [s, 3 H, $Si(CH_3)_2t$-Bu], 0.19 [s, 3 H, $Si(CH_3)_2t$-Bu], 0.90 [s, 9 H, $SiMe_2C(CH_3)_3$], 1.55 (m, 2 H, H9), 1.77, 1.93 (2 × m, 2 × 1 H, H10), 1.82, 2.16 (2 × m, 2 × 1H, H2), 1.84, 2.02 (2 × m, 2 × 1 H, H3), 2.49, 2.70 (2 × m, 2 × 1 H, H1), 2.60, 2.77 (2 × m, 2 × 1 H, H7), 2.62 (m, 2 H, H8) ppm. ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = –4.9, –4.0 [$Si(CH_3)_2t$-Bu], 17.1 (C2), 18.4 ($SiMe_2CMe_3$), 22.4 (C10), 22.5 (C9), 25.2 (C1), 25.9 [$SiMe_2C(CH_3)_3$], 26.4 (C8), 28.4 (C7), 31.9 (C3), 70.2 (C4), 127.3 (C4′), 127.7 (C2′), 129.0 (C10a), 129.1 (C1′), 129.3 (C3′), 141.1 (C6a), 144.9 (C10b), 153.1 (C4a), 155.6 (C6) ppm. GC-MS: *m/z* (%) = 393 (1) $[M]^+$, 336 (100), 262 (11), 75 (15). IR (neat): 3050.3 (w), 2925.8 (s), 2853.4 (m), 1571.9 (m), 1558.2 (m), 1471.4 (m), 1460.5 (m), 1451.9 (m), 1416.5 (m), 1358.8 (m), 1252.4 (m), 1068.0 (s), 1021.2 (s), 957.7 (s), 878.2 (s), 830.3 (s), 769.8 (s), 742.1 (s), 695.5 (s) cm^{-1}. Anal. Calcd for $C_{25}H_{35}NOSi$: C, 76.28; H, 8.96; N, 3.56. Found: C, 75.45; H, 8.89; N, 3.31.

4-(*tert*-Butyldimethylsilyloxy)-6-(trimethylsilyl)-1,2,3,4,7,8,9,10-octahydrophenanthridine (11)
Yellowish solid; mp 58 °C. R_f = 0.60 (PE–Et_2O = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.06 [s, 3 H, $OSi(CH_3)_2$], 0.24 [s, 3 H, $OSi(CH_3)_2$], 0.34 [s, 9 H, $Si(CH_3)_3$], 0.90 [s, 9 H, $OSiMe_2C(CH_3)_3$], 1.68–1.88 (m, 6 H, 3 × CH_2), 1.97–2.14 (m, 2 H, CH_2), 2.38–2.68 (m, 4 H, 2 × CH_2), 2.82 (m, 2 H, H3), 4.82 (s, 1 H, H4) ppm. ^{13}C NMR (100.5MHz, $CDCl_3$): δ = –4.9, –4.0 [$OSi(CH_3)_2$], 0.03 [$Si(CH_3)_3$], 16.9, 18.3, 22.5, 22.6, 25.3 (5 × CH_2), 25.9 ($OSiMe_2CCH_3)_3$), 26.0 [$OSiMe_2CCH_3)_3$], 28.4 (CH_2), 32.0 (C3), 70.3 (C4), 129.7, 137.4, 141.9 (C7, C10a, C10b), 153.5, 162.6 (C4a, C6) ppm. GC-MS: *m/z* (%) = 389 (1) $[M]^+$, 374 (4) [M – Me]$^+$, 332 (100) [M – *t*-Bu]$^+$, 316 (5) [M – TMS]$^+$, 258 (9) [M –

OTBS]$^+$, 242 (12), 73 (26), 57 (13). IR (neat): 2943.7 (m), 2928.1 (m), 2854.9 (m), 1558.5 (w), 1542.6 (w), 1470.9 (m), 1243.9 (s), 1076.3 (s), 1033.2 (s), 826.8 (s), 775.8 (s) cm^{-1}. Anal. Calcd for $C_{22}H_{39}NOSi_2$: C, 67.80; H, 10.09; N, 3.59. Found: C, 67.33; H, 10.15; N, 3.25.

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